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In re Application of)
)
Emanuela Mundo and James L. Kennedy)
)
) Art Unit: 1647
)
Serial No.: **10/075,249**) Examiner: Johnalyn D. Lyles
)
Filed: **February 15, 2002**)
)
For: **Detection of Antidepressant Induced Mania**)

Commissioner of Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
U.S.A.

Dear Sir:

DECLARATION UNDER 37 CFR 1.132 OF JAMES L. KENNEDY

I, James L. Kennedy, do declare and state that:

1. I am an inventor named in the above-referenced patent application.

2. I am a co-author along with E. Mundo, M. Walker, H. Tims and F.M. Macciardi on the Abstract entitled "The Role of Serotonin Transporter Gene in Antidepressant-Induced Mania in Bipolar Patients" that was published in Biological Psychiatry, 2000, 47:1355 (hereinafter "the Abstract").

3. E. Mundo is a co-inventor of the above referenced patent application. M. Walker, H. Tims and F.M. Macciardi are not inventors of the above referenced patent application.

4. M. Walker is a lab technician who did genotyping. H. Tims is a research assistant who assessed patients. F.M. Macciardi is a biostatistician who reviewed one statistical analysis of the data. They acted under the overall direction of me or co-inventor Mundo.

5. The present Declaration is to confirm that M. Walker, H. Tims and F.M. Macciardi are not inventors of the above referenced patent application.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that wilful false statement and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the application or patent resulting therefrom.

May 12/05
DATE

JAMES L. KENNEDY

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100 | **440. The role of serotonin transporter gene in antidepressant-induced mania in bipolar patients**
Biological Psychiatry Volume: 47, Issue: 8, Supplement 1, April 15, 2000, pp. S135
Mundo, E.; Walker, M.; Tims, H.; Macciardi, F.M.; Kennedy, J.L.

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61 | **Effect of acute intravenous clomipramine and antiobsessional response to proserotonergic drugs: is gender a predictive variable?**
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58 | **Linkage disequilibrium between dopamine D1 receptor gene (DRD1) and bipolar disorder**
Biological Psychiatry Volume: 52, Issue: 12, December 15, 2002, pp. 1144-1150
Ni, Xingqun; Trakalo, Joseph M.; Mundo, Emanuela; Macciardi, Fabio M.; Parikh, Sagar; Lee, Lisa; et. al.

440. THE ROLE OF SEROTONIN TRANSPORTER GENE IN ANTIDEPRESSANT-INDUCED MANIA IN BIPOLAR PATIENTS

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The induction of mania with antidepressants is an important problem in the clinical management of Bipolar Disorder (BP). Up to now no candidate genes for this phenomenon have investigated. The serotonin transporter (5HTT) is the selective site of action of serotonin reuptake inhibitors (SRIs) commonly used to treat bipolar depression. The 5HTT gene has a functional polymorphism in the promoter region (SCL6A4) consisting of 44bp insertion/deletion. The long variant (*l*) has been found to be more functional than the short one (*s*). The aim of the study was to investigate for the role of the SCL6A4 in the antidepressant induced mania in BP. A sample of 94 patients with a diagnosis of Type I or Type II BP, with at least one depressive episode treated with SRIs, and for whom genotypes of the SCL6A4 were available was investigated. The sample was then divided in two subsamples according to the presence/absence of antidepressant-induced manic episodes, as defined following the DSM-IV criteria. We found that 76 patients have had only spontaneous manic episodes (manic episodes not related to the administration of antidepressants) (SRIs−) and 18 patients (19%) have had at least one manic episode induced by SRIs (SRIs+). The allelic association analysis showed that among SRIs+ patients there was an excess of the *s* allele (chi-square = 14.3333, df = 1, p = .0001). The association analysis performed with the genotypes was also significant, showing a higher rate of heterozygous and even higher of homozygous for the *s* variant among SRIs+ patients (chi-square = 14.140, df = 2, p = .001). While these pilot results are very interesting, they need to be replicated on larger samples.

441. BIPOLAR DISORDER: DOPAMINE GENES ASSOCIATION STUDY

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Family, twin and adoption studies have shown strong evidence for the involvement of genetic factors in the susceptibility to develop bipolar disorder. Several lines of evidence indicate the dopaminergic (DA) system genes as candidates in bipolar disorder. In order to investigate DA genes in bipolar disorder we studied the DA receptor D3 gene (*DRD3*) and dopamine receptor D4 gene (*DRD4*). Both genes are highly expressed in the mesocorticolimbic DA system and their alleles code for receptor variants having small but significantly different biological properties *in vitro*. We genotyped *DRD3* and *DRD4* in 149 triad families containing probands with DSM-IV bipolar disorder and their biological parents. Statistical analysis, using extended Transmission Disequilibrium Test, showed no evidence of linkage disequilibrium between the *DRD3* alleles and bipolar disorder ($\chi^2 = 0.627$; df = 1; p = 0.42). On the other hand, the results from the analysis of the 48-bp repeat alleles of *DRD4* have shown that the 2-repeat of *DRD4* is not-transmitted a significantly more frequently to bipolar patients (29 times non-transmitted vs 9 transmitted; $\chi^2 = 10.5$; df = 5; p = 0.0012). These results indicate that the 2-repeat of *DRD4* may have a protective role for developing bipolar disorder in our sample. We are exploring this finding in greater detail by examining its relationship with narrower phenotypes including age of onset, measures of psychosis, and treatment response.

442. THE SEGREGATION OF HOPA MUTATIONS WITH HYPOTHYROIDISM IN A COHORT OF SCHIZOPHRENIC FAMILIES

R.A. Philibert (1), A.B. Smith (2), K. Razi (2), J. Stewart (2), Z. Wang (1), H.K. Sandhu (1), L.E. DeLisi (2)

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In prior studies of schizophrenia, both an increased incidence of hypothyroidism in the first degree relatives of schizophrenics and weak evidence of linkage to Xq have been reported. In an attempt to explain these findings, 111 probands with schizophrenia including 53 with a family history of hypothyroidism were examined for mutations in an Xq13 gene named HOPA that codes for a thyroid receptor associated protein and that has been associated with an X-linked mental retardation syndrome. Four males and two females were found to have variations in exon 42 of the HOPA gene. Each of the subjects had a maternal (n = 3) or personal (n = 3) history of hypothyroidism ($p < 0.009$). Although the family members with the exon 42 variation tended to experience more of a variety of illnesses including alcoholism, depression and schizophrenia, none of the associations were statistically significant. In particular, although the exonic variations were found more commonly in schizophrenics, they did not segregate significantly with respect to psychotic status. Furthermore, although the male probands with the variations tended to have poorer prognoses, no cases of mental retardation were observed. These findings replicate a prior association of hypothyroidism with HOPA mutations and suggest a genetic basis for increased incidence of hypothyroidism in first-degree relatives of schizophrenics. They also suggest that HOPA polymorphisms may have pleiotropic effects, the psychiatric phenotypic spectrum may be broad and relatively non-specific and that further studies of the role of this gene in psychiatric illness are merited.

443. A CONTROLLED FAMILY STUDY OF EARLY-ONSET OBSESSIVE-COMPULSIVE DISORDER

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Department of Psychiatry, University of Michigan

The goal of the study was to assess the familiality of early-onset obsessive-compulsive disorder (OCD). All available first-degree relatives of probands with early-onset OCD (n = 35) and controls with no psychiatric diagnosis (n = 17) were directly interviewed with two structured interviews, including one that assessed in detail the lifetime occurrence of obsessive and compulsive symptoms. Parents were also interviewed to systematically assess the family psychiatric history of all first-degree and second-degree relatives. Best-estimate lifetime diagnoses were made using all available sources of information according to DSM-III-R criteria. The rates of OCD and subthreshold OCD were significantly higher in the first-degree relatives of OCD probands than in

Medicaid in State Hospitals

To the Editor: In the article in the March issue on changing characteristics of schizophrenic patients admitted to state hospitals, the conclusions drawn by Thompson and associates (1) are weakened considerably by a significant oversight involving the funding of care in state psychiatric hospitals.

By law, Medicaid will not reimburse freestanding psychiatric hospitals for care provided to patients between the ages of 21 and 64. Therefore, the low percentages of state hospital care funded by Medicaid are not a result of a deteriorating economic situation for patients but rather reflect current constraints on reimbursement. Had this same patient population been treated in general-hospital-based psychiatric units that do receive Medicaid reimbursement for the 18-to-21 age group, the percentage of patients covered by Medicaid might be up to four times higher.

My conclusion is that rather than pour additional funding into antiquated institutions, we should promote downsizing of state facilities through the aggressive development of smaller community-based psychiatric units in local general hospitals. Such units can provide better-quality care, help keep the patient closer to home, and expand the use of partial hospitalization. They can improve the financial situation at the state level by reducing the cost of operating state hospitals while increasing the amount of federal Medicaid matching funds flowing into the state and to the general hospitals (2).

ROBERT A. PREHN, PH.D.

Dr. Prehn is administrator of the Oaks, the psychiatric hospital of the New Hanover Regional Medical Center in Wilmington, North Carolina.

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In Reply: In our article we used no-pay status as a proxy for medical indigence. No-pay status increased among both white and African American state hospital patients with a diagnosis of schizophrenia over the time period studied. Our conclusions are based in part on this information. The proportional use of Medicaid changed little, and Medicaid use was not the basis for any of our conclusions.

As for Dr. Prehn's conclusions, we have no problem with the use of general hospital units and day treatment facilities for the treatment of schizophrenia. Our point was that schizophrenic patients admitted to state hospitals are increasingly medically indigent. At the same time, indigent schizophrenic patients in other types of hospital are few in number. (Eighty-nine percent of no-pay schizophrenic patients are admitted to state hospitals.) When general hospitals are more willing to admit indigent schizophrenic patients, a discussion about further downsizing state hospitals might be appropriate. We also take exception to Dr. Prehn's assertion that the care in general hospitals has been shown to be of higher quality. Work demonstrating the accuracy of this statement has yet to be done.

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Drug-Induced Mania

To the Editor: We were greatly interested in a report recently published elsewhere about drug-induced mania in obsessive-compulsive patients (1). During the last year we observed drug-induced mania in some patients treated with clomipramine, fluoxetine, and fluvoxamine in our Obsessive-Compulsive Disorder Center in Milan.

Comorbidity appears to be important in the development of this complication. The frequent co-occurrence of affective syndromes, of a positive family history for mood disorder, or both (2) suggests that these are risk factors for developing manic or hypomanic symptoms.

Our observations indicate a definite temporal relationship between obsessive-compulsive and manic symptoms; the development of hypomanic or manic symptoms follows the progressive reduction of obsessive-compulsive symptoms. Moreover, the assessment of obsessive-compulsive patients for personality disorders revealed the presence of borderline personality disorder in 3.3 percent of such patients (3). When these patients were treated with proserotonergic antiobsessional drugs, they experienced reduced impulse control, dysphoria, and increased aggressiveness and reckless acts, symptoms similar to those found in mania.

In obsessive-compulsive patients with borderline personality disorder, psychomotor activation appears in the first weeks of treatment, before obsessive symptoms are reduced, and the clinical picture is characterized by expansive mood with claiming ideation, recurrent episodes of reduced impulse control, and loss of insight. Obsessions and compulsions remain unchanged, with a worsening of global functioning.

We agree with Stein and associates' suggestion (4) that the syndromes described are the phenomenological expression of a serotonergic dysfunction, even though data about biological and clinical correlates of serotonergic function deficit seem to be contradictory. Although reduced impulse control and aggressiveness have been explained as consequences of a serotonergic deficit, treatment with proserotonergic agents seems, in our clinical observation, to worsen these symptoms, at least in patients with obsessive-compulsive disorder.

Considering the clinical characteristics of the antidepressant-induced symptoms observed, we treat such symptoms with carbamazepine (5) or lithium. For patients who seem to be at risk of developing hypomanic or manic symptoms because of previous affective episodes or family history and personality profile, pharmacological management involves a slower increase of the dosage of proserotonergic antidepressants, combination of such drugs with stabilizing

agents from the beginning of treatment, or use of both approaches.

Systematic investigations are needed to confirm that the presence of borderline personality disorder in obsessive-compulsive patients predisposes such patients to antidepressant-induced side effects and to identify other factors.

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Drug Use by Day Patients

To the Editor: The report by Cohen and Henkin (1) in the February issue on the prevalence of substance abuse by seriously mentally ill patients in a partial hospital program encouraged me to look at my own day treatment program at the Walter P. Carter Center, a small state hospital in inner-city Baltimore. The hospital serves a socially disadvantaged catchment area that appears to be similar to the one described by the authors in inner-city Philadelphia.

Out of a total of 42 active patients in the day treatment program, I reviewed the charts of 28 patients whom I had personally examined, or 66 percent. Fourteen of the 28 patients were men and 14 were women. They ranged in age from 24 to 63 years, with mean age of 39.4. Fifty-four percent were African American, 54 percent had completed the 12th grade, and 54 percent had been jailed at least once. All were unemployed. All had been hospitalized for psychiatric disorders, most within the last six months.

Twenty-four of the 28 patients, or 86 percent, had psychotic diagnoses based on *DSM-III-R* criteria. Of these patients, ten had a diagnosis of schizophrenia, eight of schizoaffective disorder, four of bipolar disorder, and one each of major depressive disorder with psychotic features and psychotic disorder not otherwise specified.

Four patients had nonpsychotic diagnoses; three had dysthymic disorder and one had multiple personality disorder with affective symptoms. Although none of the patients had a diagnosis of personality disorder alone, 13 had a personality disorder accompanied by another disorder, and in five patients personality disorder was very prominent.

Sixteen of the 28 patients, or 57 percent, were also substance abusers. Alcohol, by far the most common substance of abuse, was the preferred or only drug of 12 of the 16 patients. Six of the 16 patients used a variety of substances, including alcohol, marijuana, opiates, cocaine, and inhalants.

Cohen and Henkin (1) found that age and diagnosis were significant in differentiating substance users from nonusers. In this sample, which was older than theirs and had a higher proportion of women, gender and diagnosis predicted substance abuse. Thirteen of the 14 men were substance abusers, compared with three of the 14 women. Half of the 24 patients with psychotic diagnoses were substance abusers, as were six of the eight patients with mood disorder (bipolar, major depressive, or dysthymic disorders).

Ten of the 13 patients with any personality disorder, four of the five patients with very prominent personality disorder, and all four of the patients with nonpsychotic disorders were substance abusers. Therefore, although substance abuse was prom inent across diagnoses, these da corroborate Cohen and Henkin findings that substance abusers ten to have diagnoses of either persona ity disorder or affective disorder.

These data also confirm Coh and Henkin's findings that "a signi icant number of patients who atte partial hospitals in urban areas cou also be abusing street drugs and alc hol." We have tried to meet th challenge by integrating the ho pital's addictions services progra into our day treatment program.

Our program is flexible enou that drug abusers can participate substance abuse groups and in ind vidual addictions counseling. The can also attend Alcoholics Anon mous and Narcotics Anonymou meetings in the building and th community. Breath analysis tests ar urine drug screens are done routine on some patients. Disulfiram is use selectively. Contacts with outsid sources of information, such as fami members or other care providers, a pursued. The patient governmen places sanctions on patients who a tend the program when intoxicated Problems certainly remain, such a the occasional need for acute detox fication and residential rehabilitatio beds. It is difficult but clearly impo tant to consider both the individu needs of certain patients and th needs of a program that serves a di verse group.

DANIEL D. STORCH, M.D.

Dr. Storch is assistant professor of psych atry at the University of Marylan School of Medicine in Baltimore.

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Hospitalphilia

To the Editor: Geller's approach (1 to the treatment of revolving-doo patients with "hospitalphilia," de scribed in the February issue, ha much to offer. If we believe that pa tients can help themselves improv why do we reject the notion that the

Behavioral Side Effects in Obsessive-Compulsive Patients Treated With Fluvoxamine: A Clinical Description

Editors:

In the recent literature, there are reports of behavioral changes, such as disinhibition (without concurrent hypomania), in patients with panic attack disorder treated with high doses of fluovaxamine or fluoxetine.[1] In the last 2 years, 250 obsessive-compulsive disorder (OCD) patients have been referred to our department. About 50% were treated with clomipramine; the others were treated with more selective serotonin reuptake inhibiting antidepressant agents, such as fluvoxamine and fluoxetine.

We have recently observed behavioral and mood changes, such as motor activation, impulse dyscontrol, aggression, and dysphoria, in a small group of patients treated with fluvoxamine. The clinical and epidemiologic data about these five patients are given in Table 1.

The symptoms seem to be a consequence of the pharmacologic treatment because all patients who developed them had been treated with high doses of fluvoxamine and the behavioral and mood changes appeared as the dosage was increased. All of the patients became aggressive and developed impulse dyscontrol when taking doses of 200 mg/day or higher. This was apparently not related to the rapidity of the dose increases, because all patients reached high doses but not within the same period of time (from 10 to 90 days).

All five of these patients are men although women are prevalent in our entire sample of 250 OCD patients (54.2%), and four of the five have symmetry, exactness, or arranging as prominent OCD symptoms. None of these five patients has a codiagnosis of Tourette syndrome or tic disorders, and the only comorbid axis I disorder was panic attack disorder, found in one patient. All patients have at least one personality disorder, as diagnosed by the Structured Interview for DSM-III-R Personality;[2] cluster C diagnoses were the most frequent (found in three patients). Three patients were found to have relatives with mood disorder (MD): one bipolar (third-degree relative) and two unipolar (first- and second-degree relatives). Studies about the comorbidity of OCD with MD have found prevalences ranging from 32.3 to 80%,[3-5] and because three of our five patients have family histories positive for MD, it can be hypothesized that the symptoms observed are the onset of a comorbid bipolar disorder elicited by fluvoxamine therapy. However, the fluvoxamine-induced side effects described above did not satisfy diagnostic criteria for major affective episodes according to the DSM-III-R classification. In addition, the presence of aggression and impulse dyscontrol as prominent symptoms can be explained as an expression of a latent serotonergic dysfunction[6] elicited by treatment with a serotonin-specific reuptake inhibitor such as fluvoxamine.

Because the pharmacologic treatment of OCD requires long-term therapy with high doses of antidepressant agents, it was not possible to stop giving fluvoxamine, only to reduce the doses. We added carbamazepine, always at doses that

TABLE 1. Clinical and epidemiologic characteristics of the sample[a]

Patient no.	1	2	3	4	5
Sex	M	M	M	M	M
Age (years)	24	27	21	31	17
Age of onset (years)	17	8	19	24	12
Axis I codiagnoses	None	None	PAD	None	None
Tic disorder	None	None	None	None	None
Family history	MD	MD	MD	OCD	Tic disorder
Personality assessment	Dep, BDL (traits)	Dep, Avoi, Passive-aggressive	Para, OCD	NOS	NOS
Obsessions	Aggressive contamination	Contamination, symmetry/exactness	Symmetry/exactness with magical thinking	Symmetry/exactness with magical thinking, somatic	Symmetry/exactness with magical thinking, Religious
Compulsions	Checking	Washing, counting	Arranging	Checking, arranging	Arranging, mental rituals
Fluvoxamine dosage (mg/day)	200	200	300	300	300
Duration of treatment before side effects (days)	15	10	18	15	90
Symptoms noted on fluvoxamine	Disinhibition, excitement, impulsiveness, tension	Aggression, suspiciousness, paranoid ideation, Early insomnia, tension	Disinhibition, aggression, dysphoria, early insomnia	Disinhibition	Aggression
Previous symptoms	Disinhibition, impulsiveness	Aggression attacks	None	None	None

[a]Abbreviations: M, male; PAD, panic attack disorder; Dep, dependent; Para, paranoid.

provided levels in plasma within the therapeutic range (4 to 12 μg/ml), for the duration of treatment.

Carbamazepine was chosen because of its rapid effect on mood changes, aggression, and impulse dyscontrol.[7] On the basis of these preliminary observations, it will be useful to collect more data about patients who develop such side effects to selective serotonin reuptake–inhibiting antidepressant agents in order to look for common clinical and, possibly, biologic characteristics related to these abnormal responses and to develop adequate pharmacologic strategies to prevent them.

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Buspirone in Combat-Related Posttraumatic Stress Disorder

Editors:

LaPorta and Ware[1] recently reported on the successful use of buspirone for the treatment of posttraumatic stress disorder (PTSD) in two patients and raised the question of whether other clinicians have had similar experiences with this agent. Buspirone, a novel anxiolytic agent with serotonin (5-hydroxytryptamine [HT])-1A-receptor partial agonist properties,[2,3] is indicated for the treatment of generalized anxiety.[4] A DSM-III-R anxiety disorder, PTSD is a syndrome of psychophysiologic sequelae to severe emotional trauma and includes symptoms in three clusters: psychologic reexperiencing of the traumatic event, avoidance of reminders of the trauma, and hyperarousal. The suggestion that buspirone may be useful for the management of PTSD symptoms[5] has been supported by recent clinical reports.[1,6] Our own clinical findings with buspirone for the treatment of PTSD in combat veterans are mixed, but they do support the claim that buspirone may be helpful for some patients with PTSD.

During the 1-year period from July 1, 1991 to June 30, 1992, we treated 12 patients with buspirone in the Hines VA Hospital PTSD Clinic. All 12 patients were male Vietnam combat veterans satisfying DSM-III-R criteria for PTSD. Two of these patients were excluded from further assessment of possible response to buspirone: one who discontinued the medication after 2 weeks, feeling it to be ineffective, and another who was already taking buspirone at the time of our initial clinical contact with him. Of the remaining 10 patients, all had previous psychiatric treatment and 8 had been previously diagnosed as having PTSD. All 10 patients were started on buspirone during the 1-year period, remained on the medication for at least 1 month, and were monitored through the end of the 1-year period or until buspirone was discontinued. Buspirone dosage was titrated gradually from 5 mg twice or thrice daily until PTSD symptoms were alleviated and the patient was stabilized, to the maximum dose tolerated, or until persistent symptoms necessitated a revision of the medication regimen. Other medications were not necessarily discontinued, but in all cases where other medications were used, there was a period of not less than a month of follow-up after starting buspirone during which clinical observations were made without further changes in the medication regimen. Patients also participated in group and individual therapy programs provided in the clinical setting. Alcohols abuse was evident in four patients during the course of treatment. Clinical outcome was assessed on the basis of firsthand clinical contact and subsequent chart review in all cases. Outcome was rated based on the global improvement item of the Clinical Global Impression (CGI) scale. Patients with global improvement scores of 1 (very much improved) or 2 (much improved) were considered to have good outcomes, patients with a score of 3 (minimally improved) were considered to have equivocal outcomes, and patients with a score of 4 (no change) were judged to have poor outcomes. For each of the patients who showed some degree of overall improvement, a further judgment was made as to whether there was any detectable improvement in each of the three PTSD symptom clusters.

Table 1 summarizes the clinical data. The patients had a mean age of 44.6 years. The mean duration of follow-up on buspirone was 4.2 months. The mean daily dose of buspirone was 46.5 mg. Four patients (40%) had good outcomes, three patients (30%) had equivocal outcomes, and three patients (30%) had poor outcomes. All seven patients who improved at least minimally showed some improvement in hyperarousal

Bipolar Disorders 2004: 6: 32–42

BIPOLAR DISORDERS

Review Article

A review of antidepressant-induced hypomania in major depression: suggestions for DSM-V

Chun BJDH, Dunner DL. A review of antidepressant-induced hypomania in major depression: suggestions for DSM-V. Bipolar Disord 2004: 6: 32–42. © Blackwell Munksgaard, 2004

Objectives: To determine if the classification of 'antidepressant-induced hypomania' in DSM-IV is supported by available data.

Methods: We reviewed the available scientific literature to examine the incidence of mania and hypomania in non-bipolar patients who were treated with antidepressants.

Results: Eighty-nine per cent of studies of antidepressants in major depressive disorder patients reported no cases of treatment-induced hypomania. No instances of treatment-induced hypomania were reported in three large studies of patients with chronic forms of depression.

Conclusions: The rate of antidepressant-induced hypomania in major depressive disorder is within the rate of misdiagnosis of bipolar depression as unipolar. Depressed patients who experience antidepressant-associated hypomania are truly bipolar.

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Key words: antidepressants – bipolar disorder – depression – hypomania

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The purpose of this review is to discuss whether the DSM-IV diagnosis of substance-induced hypomania is the correct diagnosis when applied to patients with major depressive disorder who become hypomanic in response to treatment with antidepressant medication. The notion that pharmacological substances can cause mood disturbances is widely accepted. Certain medications, particularly steroids and stimulants, can result in manic or hypomanic-like episodes in individuals who do not have a history of affective disorder (1, 2). However, as many patients with bipolar disorder begin a cycle into mania with a premanic or hypomanic depressive episode, it is possible that the application of antidepressant treatment to such patients accelerates the cycle and that the resulting hypomania or mania is not an antidepressant-induced effect but rather a tendency to amplify the natural course of illness. This review was undertaken to assess data concerning antidepressant-induced hypomania and to reflect on whether this particular classification in DSM-IV might be revised for DSM-V.

Methods

We identified all published articles investigating or citing the phenomenon of antidepressant-induced hypomania through a Medline search using the terms 'antidepressant-induced hypomania,' 'treatment-induced hypomania' and keywords 'antidepressant' and 'hypomania.' We included studies for review meeting the following criteria: presentation of data and/or discussion of the occurrence of hypomania in patients diagnosed with major depressive disorder, dysthymia, or double depression. Studies were excluded that exclusively addressed the induction of hypomania in bipolar II patients or did not identify or discriminate between the diagnoses of the patient populations receiving antidepressant therapy. The data extracted from these studies included: the incidence of antidepressant-associated hypomania in patients with unipolar depression, the diagnostic criteria used by the authors to identify patients with unipolar depression, the size of the populations studied and, where possible, the criteria used to characterize hypomanic events.

In addition, a Medline search was performed to identify all prospective trials, case reports, and drug safety surveillance data available for the following antidepressants: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, amitriptyline, desipramine, doxepin, imipramine, protriptyline, amoxapine, bupropion, maprotiline, trazodone, phenylzine, tranylcypromine, mirtazapine and venlafaxine. The root words 'adverse events' and 'hypomania' were searched with each drug name. Articles were included that presented adverse event data or reported cases of treatment-emergent hypomania in patients with major depressive disorder or chronic major depression. Articles were excluded that either did not report adverse events or did not strictly identify the diagnoses of the patient populations studied. The data extracted from these studies were as discussed above. We also reviewed the *Physicians'* Desk Reference (PDR) for adverse events data (3).

Additional data were requested from the authors of three randomized clinical trials investigating antidepressant therapy in patients with chronic forms of depression with n > 100. The number of cases of hypomania observed in each trial was obtained and is reported here.

Results

A total of 156 papers were obtained in the Medline search outlined above. Of these, 35 were excluded from the analysis: 21 reviews of drug safety surveillance data and adverse event monitoring that either did not identify patient diagnoses or did not specify which patients reported adverse events, eight reviews/meta-analyses of clinical trials and one literature review that did not identify the diagnosis of the study population, and finally two reviews of clinical trials and three controlled trials in which unipolar and bipolar patients were not distinguished.

The type and total number of studies reviewed for each antidepressant class is presented in Table 1. Of the 121 papers included in this review, a number provided data applicable to more than one antidepressant group and are included more than once in Table 1. Each of the studies applied systematic criteria to identify the affective diagnoses of the treatment groups using DSM-III, DSM-III-R, DSM-IV, Research Diagnostic Criteria (RDC), or International Classification of Diseases (ICD)-10 guidelines. We considered 'unipolar depressives' to include the DSM diagnoses of major depressive

Table 1. Studies of antidepressant-induced mania or hypomania

Antidepressant class	Total number of studies	Randomized, controlled clinical trials	Open label trials	Reviews (clinical trials and chart reviews)	Safety data and adverse event reporting	Case reports
SSRIs	80	61	5	6	0	8
Fluoxetine	32	22	3	3	–	4
Fluvoxamine	3	2	–*	1	–	–
Paroxetine	19	16	2	–	–	1
Sertraline	16	14	–	–	–	2
Citalopram	8	6	–	1	–	1
TCAs	26	22	0	4	0	0
Amitriptyline	10	9	–	1	–	–
Desipramine	–	–	–	–	–	–
Doxepin	–	–	–	–	–	–
Imipramine	15	13	–	2	–	–
Protriptyline	–	–	–	–	–	–
Heterocyclics	16	11	0	1	1	3
Amoxapine	–	–	–	–	–	–
Bupropion	7	6	–	1	–	–
Maprotiline	5	4	–	–	1	–
Trazodone	4	1	–	–	–	3
MAOIs	6	1	0	2	0	3
Phenylzine	3	–	–	2	–	1
Tranylcypromine	2	–	–	2	–	–
Other (Atypicals)	28	17	8	2	0	1
Mirtazapine	11	7	3	–	–	1
Venlafaxine	17	10	5	2	–	–

*– = No studies were identified in PubMed search. SSRI = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressant; MAOI = monoamine oxidase inhibitor.

Table 2. Cases of antidepressant-induced hypomania/mania reported in the scientific literature

Drug class	Study type (n)	Cases hypomanic switch (n)
SSRIs	60 Randomized, controlled clinical trials (6996)	0
	5 Open label trials (663)	7 [43, 73][a]
	6 Reviews of clinical trials	17 (2.5%) 'Euphoria'/1 (0.15%) 'mania' [70]
		74 (0.72%) 'Manic switch' [12]
	7 Case reports (16)	16
TCAs	22 Randomized, controlled clinical trials (1584)	5 (81)
	4 Reviews	
	3 Reviews of clinical trials +	14 (0.52%) Manic switch [12]
	1 Chart review (54)	0
MAOIs	1 Randomized, controlled clinical trial (22)	0
	2 Reviews	
	2 Chart reviews (173)	21 [80, 88]
	3 Case reports (3)	3
Heterocyclics	11 Randomized, controlled clinical trial (1868)	5 'Manic mood changes' [99]
	1 Review of clinical trials	0
	3 Case reports (3)	3
	1 Safety Data report (2482)	23 [70]
Other (Mirtazapine, Venlafaxine)	17 Randomized, controlled clinical trials (2091)	0
	8 Open label trials (1452)	2 [103]
	2 Reviews of clinical trials	9 (0.39%) Hypomania/mania [106]
		0.5% Hypomania/mania [107]
	1 Case report (1)	1

[a]Reference numbers are placed inside square brackets.

disorder (chronic, recurrent or single episode subtypes), dysthymic disorder and double depression, the RDC diagnoses of major, minor or intermittent depressive disorder, and ICD-10 diagnoses of mild-moderate depression or dysthymia. Relevant patient exclusion criteria for each study included a history of mania or hypomania, although one study included depressive patients without a history of bipolar disease within the previous year (4).

As shown in Table 2, in addition to seven case reports (5–11), only four of 71 studies (4, 11–73) investigating selective serotonin reuptake inhibitors (SSRIs) reported cases of hypomania attributed to antidepressant therapy. In a single-centre, open trial of SSRI therapy, Benazzi et al. (73) observed treatment-emergent hypomania in five of 103 (4.9%) unipolar patients presenting with a major depressive episode. Findling et al. (43) describe hypomanic switching in two of 30 (6.7%) youths receiving paroxetine, ages 5–17 years, meeting DSM-IV criteria for major depression and having no previous history of mania or hypomania, and all hypomanic symptoms 'abated without incident after drug discontinuation.' In their review of three placebo-controlled trials of citalopram, Barak et al. (70) describe 'euphoria' in 17 (2.5%) and frank mania in one (0.15%) of 682 'unipolar' patients, although they do not clarify the criteria used to classify patients as unipolar nor what symptom complex constituted 'euphoria.' Finally, in Peet's (12) analysis of data pooled from all available clinical trials of paroxetine, sertraline, fluvoxamine and fluoxetine, the calculated rate of 'manic switch' for SSRIs, including both hypomania and mania, 0.72% (74/10246), was not felt to represent a 'clinically meaningful' difference from the rate of switching in patients receiving placebo (0.21%, 8/3788). Notably, Peet acknowledges that while bipolar patients were usually excluded from trial protocols, the study population 'may not (represent) an entirely pure unipolar group,' and the 'criteria for reporting drug-induced mania may have varied' between studies (12).

Only two of 26 studies investigating tricyclic antidepressants (TCAs) (12, 19, 20, 24, 40, 56–58, 61, 63, 67, 68, 71, 74–86) report the incidence of hypomania. Kupfer et al. (81) observed hypomanic switching in both unipolar and bipolar patients with recurrent depression (RDC) who received imipramine. Five of 197 (2.5%) unipolar patients became hypomanic, with a score of 4 or greater on the Raskin mania scale and evidence of hypomanic symptoms in clinician progress notes, although four of the six total hypomanic switches in both unipolar and bipolar groups occurred *after* discontinuation of antidepressant therapy. In the same review article discussed previously, Peet also reported a manic switch rate of 0.52% (14/2716) in unipolar patients receiving TCAs, which was also not considered a clinically significant difference versus placebo (12).

We identified three articles addressing monoamine oxidase inhibitor (MAOI) therapy in unipolar depressives through our literature search (80, 87, 88), of which two reported evidence of treatment-emergent hypomania. Remick et al. (88) present the results of a retrospective chart review of patients receiving either phenylzine or tranylcypromine, in which 12 of 32 patients originally diagnosed as 'unipolar' had their diagnosis changed to bipolar following a hypomanic or manic episode. In another retrospective chart review, Rabkin et al. (80) report the incidence of hypomania, identified using RDC guidelines, in 'non-bipolar' patients meeting RDC criteria for major or intermittent depressive disorder, to be 8.3% (9/108) in patients receiving phenylzine and 0.0% (0/33) in patients receiving tranylcypromine. We also reviewed three case reports of hypomania secondary to MAOI therapy in major depressive disorder (89–91).

In addition to three case reports of trazodone-induced hypomania (92–94), only two of 13 studies of heterocyclic antidepressants (4, 37, 38, 50, 51, 62, 70, 95–100) reported cases of antidepressant-associated hypomania. Rouillon et al. (99) describe five cases of 'manic mood changes, i.e. bipolar disorders that were thought of as unipolar upon inclusion,' among 767 patients receiving maprotiline, none of whom had had a previous history of mania. The authors did not determine this rate to be statistically significant versus the rate of manic switch in patients receiving placebo (1/374). Barak et al. (70) reviewed postmarketing surveillance data for maprotiline in patients with unipolar depression by DSM-III-R criteria and described 23 episodes of mania in 2482 patients reporting adverse events (0.9%).

Hypomanic or manic switching is mentioned in only one of 10 studies (27, 45, 69, 76, 77, 101–104) we reviewed using mirtazapine in unipolar depressives. In an open-label trial of mirtazapine in 101 patients with major depressive disorder by DSM-IV guidelines, and without a history of bipolar disorder, Fava et al. (103) report only two cases of 'mania.' We also reviewed one case report of mirtazapine-induced hypomania from the literature (105). Evidence of antidepressant-associated mania is presented in two reviews of venlafaxine monotherapy. Danjou et al. (106) report an incidence rate of hypomania and mania of 0.4% (9/2258) in patients with major depression pooled from 19 studies of drug safety. Rudolph et al. (107) report a similar rate of 0.5% in 2897 total patients compiled in their review of 31 clinical trials of venlafaxine, with 'most trials exclud(ing) known bipolar' disease. No episodes of hypomania were reported in data from 15 clinical trials of

Table 3. Chronic depression: clinical trials of antidepressant therapy

Author	Study design	Subjects	Treatment	Cases of hypomania (n)
Keller et al. (1998) (57)	12-week, randomized, double-blind clinical trial	Outpatients (n = 635) meeting DSM-III-R criteria for chronic major depression (n = 294) or double depression (n = 341)	Sertraline (n = 426) versus Imipramine (n = 209)	0/426 (sertraline) 0/209 (imipramine)
Keller et al. (2000) (74)	12-week randomized, clinical trial	Outpatients (n = 681) meeting DSM-IV criteria for chronic major depressive disorder, a current major depressive disorder superimposed on a preexisting dysthymic disorder, or a recurrent major depressive disorder with incomplete remission between episodes in a patient with a current major depressive disorder and total illness duration of at least 2 years	Nefazodone (n = 225) Psychotherapy (n = 221) Combined treatment (n = 226)	0/672 (all treatment groups)
Kocsis et al. (1996) (115)	10-week open-label acute phase trial followed by 16-week open-label continuation phase for full and partial remitters followed by 2-year randomized, placebo-controlled maintenance phase for remitters	Outpatients meeting DSM-III-R criteria for dysthymia, with or without current major depression, or major depression, chronic subtype Acute phase (n = 129) Continuation phase (n = 66) Maintenance phase (n = 53)	Acute phase desipramine (n = 129) Continuation phase desipramine (n = 66) Maintenance phase desipramine (n = 28) versus placebo (n = 25)	0/129 (desipramine) 0/66 (desipramine) 0/28 (desipramine) 0/25 (placebo)

venlafaxine in unipolar depression (17, 25, 26, 30, 44, 60, 85, 102, 108–114).

The data from three large randomized clinical trials of antidepressant therapy in patients with *chronic* forms of depression (57, 74, 115) are presented in Table 3. Each study limited the patient population to only those patients meeting DSM-III-R criteria for dysthymia, chronic major depressive disorder (i.e. current major depressive episode ≥2 years with ≤2 cumulative months free of depressive symptoms), or 'double depression' (concurrent major depressive episode superimposed on antecedent DSM-III-R dysthymia) (57). Patients with a history of hypomania or mania were systematically excluded from the study protocols. We directly contacted the authors of each of these studies in order to obtain additional data concerning adverse reactions observed over the course of each trial. In all three trials, no cases of hypomanic switching occurred in either of the treatment or placebo groups over the entire duration of each study.

Table 4. Physicians' Desk Reference (3) data: antidepressant-induced switching

Drug class	PDR drug-associated adverse event data
SSRIs	
Fluoxetine	'Euphoria' = infrequent[a]
Fluvoxamine	'Manic reaction' = frequent
Paroxetine	'Manic-depressive reaction' = rare
Sertraline	'Euphoria' = infrequent
Citalopram	'Euphoria' = infrequent
TCAs	
Amitriptyline	'Euphoria' (no rate available)
Desipramine	'Hypomania' (no rate available)
Doxepin	'Shift to manic symptomatology'[b] (no rate available)
Imipramine	No adverse event data (brief listing only)
Protriptyline	'Hypomania' (no rate available)
Heterocyclics	
Amoxapine	No adverse event data (brief listing only)
Bupropion	'Euphoria' in 1.2% versus 0.5% with placebo
Maprotiline	No adverse event data (brief listing only)
Trazodone	No adverse event data (brief listing only)
MAOIs	
Phenylzine	Not listed
Tranylcypromine	'Manic symptoms' (no rate available)
Other (Atypicals)	
Mirtazapine	'Manic reaction' = infrequent
Venlafaxine	'Manic reaction' = infrequent

[a]Frequent = occurring in at least 1/100 patients;
Infrequent = occurring in 1/1000 to 1/100 patients;
Rare = occurring in <1/1000 patients.
[b]Listed under 'precautions.'
PDR = Physicians' Desk Reference.

Finally, the incidence of hypomania reported in the PDR for each antidepressant we reviewed is presented in Table 4.

Discussion

In the DSM-IV, the appearance of manic or hypomanic symptoms during treatment of a depressive episode with antidepressants is diagnosed as 'major depressive disorder with antidepressant-induced hypomania/mania.' Hypomania or mania occurring in patients taking antidepressants is widely accepted as an adverse event attributable to all classes of these medications. The rate of hypomanic or manic switching in depressed patients without a history of mania or hypomania, so-called 'unipolar' depressives, has been variably estimated as ranging from 0–11% (2, 12, 73, 80, 116), to as much as 30% in some smaller, uncontrolled studies (117). Notably, the incidence of manic switch in unipolar depressed patients receiving SSRIs has been reported by a number of authors as <1% (2, 9, 12, 73).

Considerable controversy has arisen among clinicians, however, as to whether antidepressants are truly capable of inducing hypomanic symptoms in patients with true unipolar depression (2, 12, 81, 116, 118), or if it is simply a consequence of the natural history of latent bipolar disorder (9, 73, 116, 119). This conflict of opinions is reflected in the clinical guidelines that have attempted to categorize the phenomenon. While the DSM-III-R considered antidepressant-associated hypomania as part of the 'bipolar spectrum,' DSM-IV guidelines group treatment-induced hypomania among substance-induced mood disorders, suggesting that such mood elevations are not attributable to bipolar illness itself.

Various factors may have contributed to this lack of consensus. Many of the original studies identifying antidepressant-induced mania either failed to separate true unipolar patients from bipolar patients diagnostically or took place before it was commonplace to discriminate between unipolar and bipolar affective disorder (2, 12, 81). In addition, many studies that intended to evaluate the efficacy of various antidepressant therapies did not employ systematic methods of identifying, or delineating, hypomanic and manic symptoms in their study populations (2, 81). Although all marketed antidepressants have been assessed in placebo-controlled, double-blind studies in 'unipolar' major depressive patients, the identification of hypomania in such trials is usually descriptive rather than based on established criteria and documented with rating scales. The causal relationship

between antidepressants and hypomania in depressed patients requires clarification.

The contention that antidepressants may induce hypomanic or manic symptoms, or promote rapid cycling in bipolar patients is not new, and has been frequently addressed in the literature (2, 9, 12, 73, 80, 110, 116, 119–123). The rate of manic (hypomania or mania) switch in bipolar patients reported in the literature ranges from 2.2 to 70% (73, 80, 116, 120–123), with many finding substantially higher rates of hypomanic and manic switching in bipolar patients receiving antidepressants than unipolar patients (12, 73, 80). In his study of 97 bipolar II patients receiving SSRIs or TCAs, Benazzi (73) noted hypomanic switching in 16 (17.3%) of these patients versus 4.9% of unipolar patients, while Peet (12) reported manic switching in 3.7% of bipolar patients receiving SSRIs and 11.2% of patients receiving TCAs versus 4.2% of patients taking placebo, although no distinction was made between bipolar subtypes. In a retrospective chart review spanning 60 years, Angst et al. (116) found an eightfold increase in switching in patients with a history of mania or hypomania over those without a history of mood elevation. Others have reported differences in the rates at which various antidepressants produce hypomania and mania in these patients, with TCAs promoting switching in up to three times as many cases as SSRIs (12, 120, 123). Given the greater propensity of antidepressants to induce switching in bipolar versus unipolar patients, some authors have hypothesized that individuals who experience antidepressant-emergent hypomania may represent a subset of bipolar II patients whose clinical course had previously not included a hypomanic state (73, 124).

Accurate identification of bipolar individuals among affective patients who present first with a major depressive episode is complicated by the significant overlap in symptoms of bipolar and unipolar depression. As patients may be more likely to seek medical assessment for depression than hypomania, and between 35 and 60% of bipolar patients experience depression as their initial affective episode (110, 123, 125, 126), recognizing bipolar disease is difficult at the first visit, and consequently up to 40% of patients with bipolar disorder are initially diagnosed with major depression (127). Some authors have argued that the group of patients traditionally termed 'unipolar' is likely to be composed of both 'pseudounipolars,' bipolar patients without a prior history of hypomania or mania, and the 'true unipolars' who will continue to manifest purely depressive symptoms (128, 129). Accordingly, a number of attempts have been made to identify discriminating features of unipolar and bipolar depression. Bipolar depression is characterized by an earlier age of onset and greater frequency of episodes, and associated with increased mood lability, more motor retardation, hypersomnia and hyperphagia, although no studies have demonstrated sufficient reliability in establishing the correct diagnosis (124, 126, 127, 130).

The rate of spontaneous conversion from unipolar to bipolar disease has been variably cited in the literature to be between 0 and 37.5%, with a median rate of 9.7% (126, 130). Dunner et al. (131) calculated the risk of a patient with recurrent depression becoming bipolar to be about 5%. Coryell et al. (126) found evidence of hypomanic switching in 19 (5%) of 381 patients with non-bipolar major depressive disorder during a 10-year follow-up, while Akiskal et al. (130) reported conversion to bipolar II in 8.6% of 559 patients included in an 11-year prospective study. A study of 74 young patients hospitalized for unipolar depression by Goldberg et al. (132) demonstrated a much higher incidence of spontaneous hypomania, 27% at 15 years. The available data, then, appear to suggest that the 'unipolar' patient is far more likely to undergo conversion to bipolar disease spontaneously than to experience hypomania as an adverse effect of antidepressant therapy. Although little follow-up data have been published for patients diagnosed with antidepressant-induced hypomania, the literature suggests that nearly all of these patients go on to develop bipolar disease in the future, with a spontaneously cycling course (124). Akiskal et al.'s (124) finding of the high sensitivity of 'pharmacological hypomania' for predicting bipolar outcomes lends support to the contention that antidepressant-emergent hypomania may represent acceleration of the natural course of bipolar II illness.

Community-based surveys have estimated a low lifetime prevalence of bipolar II disorder, at 1.5–2.0% (122); however, the misdiagnosis of hypomania and bipolar II disorder as recurrent major depression has likely led to global underestimation of the number of people affected in the general population (124). The diagnostic reliability of bipolar II disorder has recently been called into question, and studies have demonstrated a trend towards the significant underdiagnosis of hypomania (124, 133). Ghaemi et al. (121) report an average interval of 11.6 years from first visit to diagnosis for bipolar II patients and note that even among patients with a history of mania or hypomania prior to their initial assessment, 37% were diagnosed with unipolar major depression. Some

have attributed the underdiagnosis of bipolar II disorder to the inability of structured interviews to adequately probe the patient's history for hypomania, particularly when used in an outpatient setting (122, 133). In the French EPIDEP study, an additional 26.5% of 'unipolar' patients by DSM-IV criteria were diagnosed with bipolar II disorder when the authors used systematic structured interviews to identify hypomania during prospective follow-up (127, 134). Dunner and Tay (133) found the Structured Clinical Interview for DSM-III (SCID) was successful in identifying bipolar II disorder in only 22 of 34 patients recognized as having a history of hypomania by clinicians specially trained to make the diagnosis. Others have argued that lack of insight into bipolar disorder itself may prevent patients from seeking physician care during episodes of hypomania or mania and lead to failure in reporting previous mood elevation (125). A number of authors feel the DSM-IV guidelines themselves necessarily complicate the discrimination of bipolar disorder from unipolar depression, claiming that the 4 days of symptoms required to diagnose hypomania exceeds the average duration of these episodes (122, 127). Clearly, the accurate diagnosis of bipolar II disorder is a difficult one, particularly in individuals without a history of cycling.

The lack of consensus and clear diagnostic guidelines puts practitioners at a decided disadvantage in terms of the diagnosis and treatment of unanticipated responses to antidepressant therapy. The consequences of misdiagnosing bipolar depression as unipolar are not trivial. Overutilization of antidepressants in the management of bipolar disorder has been associated with an increased risk of drug-induced mania and the induction of rapidly cycling episodes, with a worsened disease course over the long term (2, 110, 121, 122, 125, 127). Furthermore, there is some evidence that prolonged antidepressant therapy may diminish the efficacy of future mood-stabilizer therapy in these patients (127). Consequently, many treatment recommendations have suggested that antidepressant monotherapy be avoided in bipolar patients, except in brief trials for severe depression and only in conjunction with mood-stabilizing agents (110, 125, 127). Treatment guidelines do not, however, uniformly advise the use of mood stabilizers in cases of antidepressant-emergent hypomania or mania, and not all studies have demonstrated antidepressant monotherapy to be unsafe in bipolar II depression (110, 122, 132). Some authors report that up to half of bipolar II patients have been prescribed antidepressants alone (110), and in their retrospective chart review of bipolar patients, Ghaemi et al. (125) found that one-third of bipolar patients received antidepressant monotherapy, having been initially diagnosed with unipolar depression. The result is that bipolar patients receive antidepressants far more frequently than mood stabilizers in clinical practice (121). Patients with antidepressant-emergent hypomania or mania who continue to be viewed as unipolar are likely to contribute to the size of this group.

The limitations of this review derive from the necessity to draw broad conclusions based on data compiled from a number of articles that differ in type, size and design. Each of the studies was conducted by a varying protocol and, for the most part, without the expressed goal of identifying the rate of hypomanic switching in unipolar patients. No systematic rating scales were used to document hypomania in these subjects. Furthermore, most clinical trials of antidepressants are brief (6–12 weeks) and it is possible that patients who would have experienced a desired hypomanic syndrome might have gone undetected. Many clinical trials utilize lower doses, and it is possible that a higher rate of hypomania would have been observed if higher doses were used. Additionally, it would be important to observe patients who became hypomanic while treated with antidepressants to determine if they experienced spontaneous hypomania with subsequent episodes. Differences in patient inclusion/exclusion criteria, including diagnostic criteria, illness duration, severity of disease, and presence or absence of comorbid conditions, greatly reduce the uniformity of the pooled study population. Notably, while most of the clinical trials reviewed specifically excluded patients with a history of mania or bipolar illness, a number did not clearly establish a unipolar study population beyond excluding patients with 'any other primary affective disorder.' In addition, the criteria used by the investigators to report hypomania as a treatment-related adverse event is likely to have varied between studies.

The data reviewed in this paper demonstrate that the incidence of antidepressant-induced hypomania in major depressive disorder is within the rate of misdiagnosis of bipolar patients as unipolar. Of the studies we reviewed, in which the authors made considerable effort to systematically identify and separate bipolar from unipolar patients, 89% (87/98) reported no cases of hypomania or mania following the initiation of antidepressant treatment in unipolar depressed patients. Among patients with chronic forms of depression, i.e. those having either chronic major depression, dysthymia or double depression, the authors found no evidence

of either hypomania or mania attributable to antidepressant therapy (57, 74, 115). We interpret the studies we reviewed to suggest that patients with major depressive disorder who experience mania or hypomania should be recognized as truly having a bipolar disorder and that antidepressant treatment cannot make a unipolar patient bipolar. The DSM-IV classification of antidepressant-induced hypomania in major depressive disorder under the diagnostic heading of substance-induced mood disorders thus requires re-evaluation for the DSM-V.

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Dr. Simon and Dr. VonKorff Reply

SIR: We agree with Dr. Lesser that an epidemiologic assessment such as the DIS cannot provide the same understanding as a clinical assessment. Consequently, our results do not argue against the existence or importance of alexithymia in any individual patient. In the community sample we described, however, functional somatic symptoms did not typically function as defenses against awareness of psychological distress. "Somatizers" were aware of and quite willing to report anxiety and depression.

We also agree that the distinction between psychosomatic disorders and somatization remains unclear, but we hope that our findings might sharpen it. Descriptions of alexithymic patients with classic psychosomatic diseases (hypertension, peptic ulcer) emphasize the physical consequences of denying or avoiding psychologic distress. Somatizing patients, however, usually display an increased sensitivity to all types of distress, both physical and psychological. The two groups might be regarded as lying on opposite ends of a spectrum of symptom sensitivity.

Many multisymptom patients freely acknowledge that their physical symptoms and emotional distress are interwined. Medical and mental health providers, however, may focus on or give credence to only one domain. Effective, patient-centered care will require providers and patients to integrate the physical (e.g., pain or fatigue), emotional (e.g., depressed mood or anxiety), and behavioral (e.g., reduced activity or social withdrawal) components of illness.

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Antidepressant-Induced Mania in Obsessive-Compulsive Disorder

SIR: Warren Steiner, M.D., C.M. (1), has recently reported a case of fluoxetine-induced mania in a patient with obsessive-compulsive disorder. The author's patient presented a good response to 20 mg/day of fluoxetine with regard to her obsessive-compulsive disorder but soon developed a hypomanic syndrome and her dose of fluoxetine had to be lowered. This led to the recurrence of obsessions and compulsions, but a subsequent increase to the initial fluoxetine dose plus addition of clonazepam, 0.5 mg/day, finally succeeded in keeping the patient asymptomatic of both mood and obsessive features. The author concludes that all patients treated with fluoxetine, regardless of primary psychiatric diagnosis, should be monitored for the development of mania.

A more significant finding, nevertheless, involves the fact that Dr. Steiner's patient finally remained euthymic and free of obsessive-compulsive symptoms. Antidepressant-induced mania in obsessive-compulsive patients has already been reported elsewhere (2, 3), but both reports stated the impossibility of keeping the patient euthymic without the recurrence of obsessive-compulsive disorder. We recently reported a case of recurrent clomipramine-induced mania in a patient with obsessive-compulsive disorder (4). Neither lowering clomipramine dose nor adding lithium carbonate or neuroleptics succeeded in keeping the patient asymptomatic of both mood and obsessive features. Interestingly, obsessive-compulsive symptoms remitted during the manic episode but reemerged insidiously as soon as the manic syndrome responded to treatment and/or clomipramine was lowered. During the past 3 months this patient was treated with fluoxetine, but while she did not become manic again, her severe obsessions and compulsions unfortunately were refractory to even high doses of this drug.

An inverse relationship has been postulated between obsessive-compulsive disorder and mania (3). Indeed, primary mania is an extremely rare complication of obsessive-compulsive disorder. We have suggested that abnormal regulation of brain serotonergic function might be related to at least some aspects of this supposed pathophysiological relationship (4). Since fluoxetine, a selective serotonergic antidepressant, clearly induced mania as long as obsessive symptoms improved in Dr. Steiner's patient, we might consider this hypothesis further supported. However, since that patient finally reached euthymia free of obsessive-compulsive symptoms, one might speculate that some other mechanisms and neurotransmitters should be involved. Despite its high potency inhibiting serotonin reuptake, clomipramine also has noradrenergic properties, which should be considered with regard to the previous case reports on this issue. Such cases as Dr. Steiner's illustrate that the role of antidepressants inducing mania in several types of psychiatric patients deserves further research.

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Dr. Steiner Replies

SIR: Dr. Vieta and Dr. Bernardo raise the interesting question of the relationship between mania and obsessive-compulsive disorder and of the pharmacological basis of the manic switchover in these patients. It is likely that the switchover processes in obsessive-compulsive disorder patients and in patients with mood disorders are different, as various antidepressants seem to present a different risk of development of mania when used in patients with obsessive-compulsive disorder or mood disorder. In obsessive-compulsive disorder pa-

tients treated with fluvoxamine, Jefferson et al. (1) found a 2.5% switchover, while in mood disorder patients treated with fluvoxamine a 0.6% incidence has been reported (2), indicating that patients that with obsessive-compulsive disorder may be at greater risk of developing mania. However, with other serotonin-specific reuptake blockers this dramatically increased rise for obsessive-compulsive disorder patients has not been found. Sertraline, which has been found to be ineffective in treatment of obsessive-compulsive disorder (3), has not as yet been reported to precipitate manic episodes in patients with obsessive-compulsive disorder. This lower risk of a manic switch with a medication that is ineffective in treating obsessive-compulsive disorder may in fact support the hypothesis of an inverse relationship between obsessive-compulsive disorder and mania. This relationship could also be explained by the greater selectivity for serotonin reuptake blockade compared to noradrenaline reuptake blockade found with sertraline when compared to other serotonin specific reuptake blockers (4). It is possible that a certain minimum blockade of noradrenaline reuptake is essential for treatment of obsessive-compulsive disorder as well as for the development of mania in these patients. An interesting report of the use of metergoline in reversing clomipramine-induced improvement in obsessive-compulsive disorder symptoms (5) leads one to wonder whether serotonin antagonists could also reverse antidepressant-induced mania in obsessive-compulsive disorder patients who switchover. If so, this would certainly support the hypothesis of an inverse relationship between mania and obsessive-compulsive disorder.

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Obsessive-Compulsive Disorder in Relation to Body Dysmorphic Disorder

Sir: We read with interest the recent article on body dysmorphic disorder by Katherine A. Phillips, M.D. (1). Dr. Phillips suggested that body dysmorphic disorder is related to obsessive-compulsive disorder, and that dynamic factors are also involved. We recently evaluated a patient who appeared to meet criteria for both obsessive-compulsive disorder and body dysmorphic disorder.

Ms. A was a 17 year old who presented complaining of compulsive skin picking and feared disfiguration. The patient had been experiencing intrusive and distressing images of "pus" under her skin pores for 4 years. She began to pick her skin at a mirror, using a pin to get the "pus" out. She had no concern over her skin's natural appearance, realising no one else could see the alleged problem. Nonetheless, she was unable to pass a mirror without picking her face, shoulders, back, and breasts, ultimately causing some skin changes. She would spend a half hour in the shower to undo the damage. She was unable to stop her behavior.

Six months of dynamic psychotherapy failed to relieve her symptoms. Ms. A achieved considerable insight into her symptoms. The patient's mother, a university anthropologist, had impressed upon the patient the diversity of beauty in various cultures. However, clear skin, her mother stressed, was valued throughout the world. Following this discussion, the patient experienced the intrusive images. In therapy, the patient learned how conflicted and ambivalent her relationship was with a perfectionist and controlling mother who focused on skin. Also a perfectionist, the patient became even more distressed with imagined damage she was doing to her skin.

Mental status evaluation revealed a young woman with very mild acne. She showed obvious embarrassment at her symptoms but was not able to control her compulsive skin picking. Her Yale-Brown Obsessive Compulsive Scale score was 24; Beck Depression Inventory score was 9. The patient and her parents requested behavioral therapy.

Jenike (2) suggested that compulsive face picking is a relatively rare disorder seen primarily in young women with mild acne, responding to treatments useful in obsessive-compulsive disorder. Our patient did not limit the picking to just her face but appeared otherwise similar to Jenike's patients. Our patient met full criteria for both obsessive-compulsive disorder and body dysmorphic disorder. Other reports stress that body dysmorphic disorder may respond to serotonergic antidepressants useful in obsessive-compulsive disorder (3). As Thomas (4) suggested, body dysmorphic disorder may be primary or secondary, and in our patient it appeared to be secondary to a primary obsessive-compulsive disorder. It is possible that character traits, obsessionality and perfectionism, would predispose this patient to both disorders.

From a dynamic perspective, Ms. A's mother was dominant, perfectionist, and focused on skin. The patient attempted unsuccessfully to neutralize anxiety around her conflict with her mother through repression and displacement. Intrusive images were the symptoms of this conflict, not imagined ugliness. Anxiety was defended against through classic doing and undoing. The behavior resulted in minor skin changes, about which the patient became phobic and avoidant.

We thank Dr. Phillips for her cogent discussion of the complex interrelationship between body dysmorphic disorder and obsessive-compulsive disorder. We hope our case has been helpful and illustrative.

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